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PROSPECT

Electromagnetic Initiation of Transcription at Specific DNA Sites

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Abstract Initiation of transcription by electromagnetic (EM) fields offers an insight into mechanism. EM field stimulated transcription appears to require specific DNA sequences, and these bases may be sites where EM fields generate large repulsive forces between chains by accelerating electrons that move within DNA. We can estimate the repulsion between chains by assuming that electron affinity is a measure of electron density at each base, and inversely related to the velocity of electrons (and the force). The repulsive force can be compared to the attraction between chains due to H-bonds. From the difference between repulsion and attraction, we show that sites rich in C and T, as in the specific sequences, would be more likely to come apart in EM fields. These calculations suggest a plausible mechanism for initiation of transcription by EM fields, and provide a rationale for specific sequences to function as EM field response elements. Electron flow could also be a factor in DNA chain melting due to Joule heating. J. Cell. Biochem. 81:689–692, 2001. © 2001 Wiley-Liss, Inc.

Key words: EM fields; transcription; specific DNA sequences; EM response elements

INTRODUCTION

Transcription is initiated via many different signaling pathways and by transcription factors that bind at different DNA sites. What appears to be common to all is that the reactions cause DNA chains to separate so RNA polymerase can function. The involvement of many chemical reactions makes it difficult to think in terms of a general mechanism, but the ability of relatively weak electromagnetic (EM) fields to initiate transcription [Goodman and Blank, 1998] offers an alternative approach to mechanism. As a first approximation, we can think of EM fields as generating repulsive forces that aid chain separation. Studies of acceleration of reaction rates by electromagnetic (EM) fields indicate that the fields affect electron transfer reactions [Blank and Soo, 1998, 2000], and recent observations that DNA can conduct electrons within its stacked base pairs [Wan et al., 1999; Porath et al., 2000], suggest the possibility that EM fields initiate transcription by interacting directly with moving electrons in DNA [Blank and Goodman, 1999, 2000]. The EM field forces (proportional to electron velocities) that initiate transcription in DNA are comparable to those that accelerate enzyme reactions. EM fields penetrate tissues without attenuation, so they must penetrate to the nuclear DNA and interact with the conducting electrons. Furthermore, since different DNA sequences have different conductivities [Meggers et al., 1998], EM fields could theoretically interact more strongly with specific DNA sequences. Studies of EM stimulated transcription have identified special sequences in the c-*myc* and HSP70 promoters that are required for the response to EM fields. Eight nCTCTn sequences in a 900bp region of the c-*myc* promoter [Lin et al., 1994], and three nCTCTn sequences in a 70bp region of the HSP70 promoter [Lin et al., 1998], appear to be needed [Lin et al., 2000]. We have called these nCTCTn sequences electromagnetic field response elements (EMRE). Removing EMREs eliminates the EM field response, and introducing them imparts the ability to respond to applied EM fields. (The 900bp segment of the c-*myc* promoter containing eight EMREs, when placed upstream of CAT or luciferase reporter

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constructs that are otherwise unresponsive to EM fields, induces an EM field response.) It would appear likely that the nCTCTn sequences generate especially large repulsive forces between DNA chains. In this paper, we develop the assumption that EM field interaction with electron currents in DNA can generate a force that contributes to chain repulsion, and we show how the force would be expected to vary with the base composition of DNA.

Electron Movement in DNA

In studies of DNA, electron flow has been generated by applied electric fields, light-induced electron release, etc. [Arkin et al., 1996; Dandliker et al., 1997; Meggers et al., 1998; Wan et al., 1999; Porath et al., 2000]. We do not know if electron flow occurs as a result of processes within the DNA that are part of its normal function, and if so, the nature of that flow. Electron flow could be a mechanism for testing the integrity of the DNA, or restricted segments of it, to see if breaks have occurred. Also, transcription factors may isolate segments of DNA for local electron flow as part of the mechanism for initiation of transcription by generating a force or heat, as discussed below.

To proceed, we shall assume that rapid, tonic flows of electrons within DNA are needed to coordinate reactions in different parts of the linear DNA polymer, and that electron currents flow intermittently along each DNA chain separately. Experiments show that double stranded DNA is needed for electronic conduction, but other studies show that bases from one chain can be flipped out of the double helix while the second chain is virtually unaffected, suggesting independent function of the two chains [Klimasauskas et al., 1994]. In any case, if we assume independent conduction in each chain, it is possible to have a circuit of the two DNA chains that includes the entire molecule. It is also possible to conceive of repulsive forces generated by the EM fields when currents flow in opposite directions in a circuit made up of the two chains.

Evaluating the effects of electronic conduction in DNA along the lines of classical physics, the forces generated by EM fields will be proportional to the velocity, v, of the electrons, as given by the Lorentz equation, $F = qvB$, where q is a unit charge and B is the strength of the magnetic field. Assuming independent conduction in each chain, we estimate the relative repulsive force between chains generated by an EM field and compare it to the strength of H-bonding holding the chains together at that base. From the difference we can determine how that base would be affected by an EM field. We use the electron affinity of the different bases to estimate the local electron density, and estimate the velocity at each base in terms of the distribution of electrons. The forces should depend on the properties of the constituent bases, and hence on the detailed DNA composition.

DNA Chain Repulsion Model

We calculate the forces of repulsion between chains due to EM fields, assuming that the electron affinity is a measure of the electron density at each base. That is, in a population of delocalized electrons, there will be a higher relative concentration (density) at the base with the greater electron affinity. The values we use for electron affinity at each base [Chen and Chen, 1998] are as follows: $A = 0.97$, $G = 1.51$, $T = 0.81$, $C = 0.57$, and we assume that electron affinities are directly proportional to the local charge density. When a current flows through the DNA, the charge carriers must move faster when there are fewer of them, so we estimate that the relative electron velocity at each point is inversely related to electron density. It is the electron velocity, v, that determines the force, F, for a particular value of EM field.

To estimate the forces of attraction between chains, we assign known H-bond interaction energies for A-T and C-G bonds. A-T bonds have two H-bonds (N-H-N, N-H-O) for a total of $\sim$10 kcal/mol, and C-G bonds have three H-bonds (N-H-N, N-H-O, O-H-N) for a total of $\sim$15 kcal/mol, so C-rich chains have greater attraction. The importance of C-G bonds in raising the DNA chain melting point is well known.

In these calculations, we consider individual bases, but electrons are delocalized and a better approximation would average adjacent electron affinities over n bases ($3 < n < 10$). This more realistic electron distribution over a length of DNA would provide a better estimate of the probability of opening a turn of the DNA helix. Obviously, the average would consider attractive as well as repulsive forces.

Estimating Force Balance

Table I provides an estimate of the relative repulsive force and relative attraction energy at

TABLE I. Steps in Calculating Force Balance

	Bases	C	T	A	G
1	Electron affinity (EA)	0.57	0.81	0.97	1.51
2	Repulsive force$\sim$ Velocity$\sim$ $(EA)^{-1}$	1.75	1.25	1.03	0.66
3	Attraction$\sim$H-bonds	3	2	2	3
4	Attraction$\sim$H-bonds	1.5	1	1	1.5
5	Repulsive force-attraction	0.25	0.25	0.03	−0.84
6	Net effect	repulsion	repulsion	—	attraction

each of the four bases, as outlined in the above section. Since the values are relative, no units are given. The first line lists values of the electron affinity for each of the four bases. The second line takes the inverse of the electron affinity to estimate the relative electron velocity at each base, since the velocity should be inversely related to the concentration. The electron velocity is directly proportional to the force generated by an EM field at each base. Obviously, the magnitude of the repulsive force would increase as the EM field strength increased. The third line lists the number of H-bonds, which is apportioned between the two bases in a pair and listed in the fourth line. The fifth line calculates the difference between the estimated repulsive forces and attraction energy at each base. The net effect, repulsion or attraction, is listed on the sixth line.

Our calculations show that sites rich in C and T would be more likely to come apart when repulsive forces are generated by EM fields. This provides a rationale for our identification of electromagnetic response elements (EMREs) associated with the response of the c-myc and HSP70 promoters to EM fields. In those studies, we identified eight nCTCTn elements in c-myc and three in HSP70 that were needed for the response. In later studies, we incorporated the 900bp segment of the c-*myc* promoter, with its eight EMREs, upstream of CAT or luciferase reporter constructs that were otherwise unresponsive to EM fields, and induced an EM field response.

DNA Chain Melting

The above EM field mechanism may provide insight into other transcription mechanisms, since it focuses on the structurally based attractive and repulsive forces that are involved in any process of chain separation. The attractive forces are those due to H-bonds, and if the processes generally initiated by chemical reactions weaken attractive forces by processes that depend on electronic conduction, then the EM field mechanism may be relevant. DNA chain melting (i.e., disruption of intermolecular bonds due to greater molecular motion) may be such a process.

Let us assume that DNA chain melting results from Joule heating due to electronic currents that are generated by reactions involving transcription factors. Using the same approach as with EM fields, we assume electron affinity is a measure of the electron density at each base, and that electron affinities are proportional to the local charge density. We estimate that the electrical resistance (R) at each base is inversely related to electron density. That is, the resistance is greater when there are fewer electrons to function as charge carriers. Since the current (I) would be the same at all points along the DNA, the heating associated with local electron flow (I^2R) will vary with the value of R. Obviously, the greater the heating, the greater the possibility of causing local DNA melting. Here too, as a first approximation, C-rich chains should have higher resistances and higher attractive forces, but the detailed code will be needed to give the effect on different regions of the DNA.

It would appear that calculations of the velocity, v, and the resistance, R, are closely related, since they are similarly derived from the electron affinities in our model. Therefore, the reasoning based on chain repulsion (an EM field mechanism) or chain melting (a more general mechanism) would lead to similar conclusions.

CONCLUSION

The calculations in this paper suggest a plausible mechanism for initiation of transcrip-

tion by the generation of repulsive forces between DNA chains when EM fields interact with flowing electrons. They also provide a rationale for the ability of the EMREs, in the two promoters we have studied, to function as EMRE's.

In addition to the response to EM fields, electron flow may be involved in other processes in DNA. For this reason, the approach of this paper may be useful in relating the details of DNA sequence to function. It would be interesting to see if a map of estimated electronic velocities (or resistances) correlates with a DNA function map, i.e., if regions that favor chain separation correlate with regions associated with control of DNA transcription as opposed to coding regions.

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REFERENCES

Arkin MR, Stemp EDA, Holmlin RE, Barton JK, Hormann A, Olson EJC, Barbara PF. 1996. Rates of DNA-mediated transfer between metallointercalators. Science 273:475–480.

Blank M. 1995. Na/K-adenosine-triphosphatase. Adv Chem 250:339–348.

Blank M, Goodman R. 1997. Do electromagnetic fields interact directly with DNA? Bioelectromagnetics 18: 111–115.

Blank M, Goodman R. 1999. Electromagnetic fields may act directly on DNA. J Cell Biochem 75:369–374.

Blank M, Goodman R. 2000. Coupling of low frequency electromagnetic fields to activate DNA: stimulation of the cellular stress response. IEEE Trans Plasma Sci 28: 168–172.

Blank M, Soo L. 1998. Enhancement of cytochrome oxidase activity in 60Hz magnetic fields. Bioelectrochem Bioenerg 45:253–259.

Blank M, Soo L. 2001. Electromagnetic acceleration of electron transfer reactions. J Cell Biochem 81:278–283.

Chen ES, Chen ECM. 1998. A proposed model for electron conduction in DNA based upon pairwise anion π stacking: electron affinities and ionization potentials of the hydrogen bonded base pairs. Bioelectrochem Bioenerg 46:15–19.

Dandliker PJ, Holmlin RE, Barton JK. 1997. Oxidative thymine dimer repair in the DNA helix. Science 275: 146–167.

Goodman R, Blank M. 1998. Magnetic field stress induces expression of *hsp70*. Cell Stress and Chaperones 3: 79–88.

Klimasauskas S, Kumar S, Roberts RJ, Cheng X. 1994. Hhal methyltransferase flips its target base out of the DNA helix. Cell 76:357–369.

Lin H, Goodman R, Henderson AS. 1994. Specific region of the c-*myc* promoter is responsive to electric and magnetic fields. J Cell Biochem 54:281–288.

Lin H, Blank M, Goodman R. 1999. Magnetic field-responsive domain in the human HSP70 promoter. J Cell Biochem 75:170–176.

Lin H, Blank M, Goodman R. 2001. Regulating genes with electromagnetic response elements. J Cell Biochem 81:143–148.

Meggers E, Michel-Beyerle ME, Giese B. 1998. Sequence dependent long range hole transport in DNA. J Am Chem Soc 120:12950–12955.

Porath D, Bezryadin A, deVries S, Dekker C. 2000. Direct measurement of electrical transport through DNA molecules. Nature 403:635–638.

Wan C, Fiebig T, Kelley SO, Treadway CR, Barton JK. 1999. Femtosecond dynamics of DNA-mediated electron transfer. Proc Natl Acad Sci USA 96:6014–6019.